General

Guideline Title

Diagnosing prostate cancer: PROGENSA PCA3 assay and Prostate Health Index.

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Diagnosing prostate cancer: PROGENSA PCA3 assay and Prostate Health Index. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Jun 2. 50 p. (Diagnostics guidance; no. 17).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

The PROGENSA PCA3 assay and the Prostate Health Index are not recommended for use in people having investigations for suspected prostate cancer, who have had a negative or inconclusive transrectal ultrasound prostate biopsy.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Prostate cancer

Guideline Category

Diagnosis

Technology Assessment

Clinical Specialty

Internal Medicine

Oncology

Pathology

Urology

Intended Users

Advanced Practice Nurses

Clinical Laboratory Personnel

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To evaluate the clinical effectiveness and cost-effectiveness of using the PROGENSA PCA3 assay or the Prostate Health Index (PHI) in conjunction with clinical assessment and other investigations to determine if people having investigations for prostate cancer need a second biopsy

Target Population

Men with suspected prostate cancer, for whom a repeat biopsy is being considered following a negative or inconclusive transrectal ultrasound prostate biopsy

Interventions and Practices Considered

PROGENSA PCA3 assay and Prostate Health Index (PHI)

Major Outcomes Considered

- Analytic validity outcomes
  - Measures of consistency and accuracy between, and within, laboratories such as coefficient of variation
  - Sensitivity and specificity against external standard
  - Assay robustness
  - Test failure rate
- Clinical validity outcomes
  - Estimates of the intervention or comparator test (means and standard deviation [SD], proportion positive) in men with positive and negative results on second biopsy
  - Specificity and sensitivity for different threshold points of PCA3, Prostate Health Index (PHI) or prostate-specific antigen (PSA)
  - Comparison of area under the curve (AUC) for different tests or test combinations
  - Gain in sensitivity and specificity estimates by adding intervention test as derived from receiver operating characteristics (ROC) curves
  - Results of logistic regression analyses

    - Test failure rate
    - Adverse effects of test or subsequent biopsies
    - Risk group and stage of cancers detected
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this diagnostic guidance and prepare a Diagnostics Assessment Report (DAR). The DAR for this diagnostic guidance was prepared by the Liverpool Reviews and Implementation Group (LRiG), University of Liverpool (see the "Availability of Companion Documents" field).

Assessment of Clinical Effectiveness

Assessing the clinical effectiveness of the PCA3 assay and Prostate Health Index (PHI) in the diagnosis of prostate cancer involved three separate systematic reviews:

1. A review of the analytic validity of the intervention tests to assess how accurately the tests measure PCA3/PHI level present in a sample
2. A review of the clinical validity (diagnostic test accuracy) of comparator and intervention pathways to assess how the addition of the PCA3 assay or PHI might contribute to the diagnosis of prostate cancer.
3. A review of the clinical utility of the intervention test pathways to evaluate how the addition of the intervention tests might affect patient outcomes, including long-term outcomes such as mortality and morbidity from prostate cancer, and intermediate outcomes such as side effects from tests.

Search Strategy: Analytic Validity Review

Electronic Databases

The following databases were searched on 28th April or 19th May 2014 for eligible studies:

- MEDLINE
- EMBASE
- CENTRAL (Cochrane Central Register of Controlled Trials)
- Health Technology Assessment (HTA) database
- CDSR (Cochrane Database of Systematic Reviews)
- DARE (Database of Abstracts of Reviews of Effectiveness)
- ISI (Institute for Scientific Information) Web of Science
- MEDION database for related diagnostic test accuracy reviews
- ARIF (Aggressive Research Intelligence Facility) database http://www.birmingham.ac.uk/research/activity/mds/projects/HaPS/PHEB/ARIF/database/index.aspx
- Prospero systematic review register (http://www.crd.york.ac.uk/PROSPERO/)

No study design filters were applied and non-English language reports were excluded. All databases were searched from 2000. The following types of report were excluded:

- Editorials, opinion pieces and correspondence on journal articles
- Conference abstracts

Trial and research registers were searched on 24th July 2014 for ongoing trials and reviews including:

- Clinicaltrials.gov (http://clinicaltrials.gov/)
- MetaRegister of Controlled Trials and ISRCTN Register
- World Health Organisation (WHO) International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/)

Details of the search strategies used can be found in Appendix 2 of the Assessment Report.

Searching Other Resources

Backward citation searching was undertaken on key review articles. As in all searches, the US Food and Drug Administration (FDA) website was searched for the following terms: PCA3, PHI, and p2PSA.

Study Selection Strategy: Analytic Validity Review

Three reviewers independently screened all titles and abstracts identified via searching and obtained full paper manuscripts that were considered relevant by any of the reviewers (Stage 1). The relevance of each study was assessed according to pre-specified inclusion criteria (Stage 2). Studies that did not meet the criteria were excluded. Any discrepancies were resolved by consensus.

The analytic validity review focused on studies that addressed the ability of the intervention test to accurately and reliably measure the target analyte. Inclusion criteria are presented in the table below.

Table. Inclusion Criteria (Analytic Validity)

Patient population	All adult men
Intervention test	PCA3 assay or [-2]pro-prostate-specific antigen (p2PSA) or Prostate Health Index (PHI) score
Outcomes	• Measures of consistency and accuracy between, and within, laboratories such as coefficient of variation • Sensitivity and specificity against external standard • Assay robustness • Test failure rate
Study design	All study designs including collaborative studies, external proficiency testing, peer-reviewed repeatability studies, internal reports and manufacturer data

Studies with precision or accuracy control data presented only as part of the Methods section of a publication, in order to describe the test that was used, were not included in the review.

Search Strategy and Study Selection Strategy: Clinical Validity Review

The same search strategy and study selection strategy were used for the analytic validity and clinical validity reviews.

Inclusion Criteria: Clinical Validity Review

Comparisons between the performance of the intervention tests (PCA3 assay and PHI) and the comparison tests (clinical assessment and magnetic resonance imaging [MRI]) can be made using either data from studies carried out in the same study population (within-study or direct comparisons) or from data from studies where intervention and comparator tests are carried out in different populations (between-study or indirect comparisons). The preferred data for this review are derived from within-study comparisons of intervention and comparator test pathways.

Within-Study (Direct) Comparisons

Due to uncertainty about the diagnostic pathways used in National Health Service (NHS) clinical practice and the limited availability of MRI scanning facilities, the External Assessment Group (EAG) initially included all studies with a direct comparison of the PCA3 assay or PHI with any one or more of following component comparator tests:

- Individual clinical risk factors such as age, digital rectal examinations (DRE)
- Standard clinical judgement/nomograms
- Prostate-specific antigen (PSA) levels
- MRI results: T2-MRI/diffusion weighted (DW)-MRI

As the intervention tests (PCA3 assay or PHI) can be used as replacement, add-on or triage tests to the comparator tests, studies that have directly compared the clinical validity of the PCA3 assay versus the clinical validity of PHI, with or without other comparators, were also included. The inclusion criteria used to select eligible within-study comparisons are presented in the Table below.

Systematic Reviews for Use in Between-study (Indirect) Comparisons

In the absence of any available within-study comparisons the EAG would have considered carrying out between-study (indirect) comparisons of the intervention tests versus comparator tests. Given the likely large number of studies evaluating each of the intervention and comparator tests, estimates of the clinical validity of the intervention and comparator tests from good quality systematic reviews with meta-analyses were sought to provide data for any between-study (indirect) comparisons undertaken. The inclusion criteria used to select eligible systematic reviews are presented in the table below.

Table. Inclusion Criteria (Clinical Validity – Direct and Indirect Studies)

Patient population	Men suspected of having prostate cancer who had had at least one negative or equivocal biopsy. The review was restricted to studies where at least six cores were taken in initial biopsy. Studies of men taking medications known to affect serum PSA levels such as finasteride (Proscar, Propecia), dutasteride (Avodart), and anti-androgen therapy (Lupron) were excluded.
Intervention	Diagnostic test or test pathway including PCA3 and/or PHI
Comparator	Diagnostic test or test pathway without PCA3 or PHI and including one or more of following comparator tests: • Individual clinical risk factors such as age or DRE • Standard clinical care/nomograms • PSA levels • MRI results: T2-MRI/DW-MRI Studies that directly compared the performance of PCA3 with that of PHI, with or without other comparators, were also included.
Reference standard	Eligible studies compared the performance of comparator or intervention pathways to a histological analysis of prostatic tissue. This could have been obtained from a second prostatic biopsy or from a prostatectomy specimen. Biopsy must have taken place within 1 year of the intervention test. Studies with all types of second biopsy were included: • Repeat standard transrectal ultrasound (TRUS) biopsy • Saturation • Template • MRI targeted biopsies • Use of prostatectomy specimens
Outcomes	Studies reporting any of the following were included: • Estimates of the intervention or comparator test (means and standard deviation [SD], proportion positive) in men with positive and negative results on second biopsy • Specificity and sensitivity for different threshold points of PCA3, PHI or PSA • Comparison of area under the curve (AUC) for different tests or test combinations • Gain in sensitivity and specificity estimates by adding intervention test as derived from ROC curves • Results of logistic regression analyses • Test failure rate • Adverse effects of test or subsequent biopsies • Risk group and stage of cancers detected
Study design	Studies reporting within-study comparison of interventions/comparators: • Paired design. Cross-sectional or longitudinal studies in which intervention test(s), comparator test(s) and reference standard test were performed in the same group of people • Unpaired design. Trials in which people were randomised to either the intervention or comparator test(s) and then all

	received the reference standard test Studies for inclusion in between-study comparisons of interventions/comparators: • Systematic reviews with meta-analyses of the clinical validity of the intervention or any of the comparator tests

Abbreviations: DRE, digital rectal examination; DW-MRI, diffusion-weighted magnetic resonance imaging; MRI, magnetic resonance imaging; PHI, Prostate Health Index; PSA, prostate-specific antigen; ROC curve, receiver operating characteristics curve; TRUS, transrectal ultrasonography.

Clinical Utility Review

The planned methods for the clinical utility review were as described in the protocol. No studies were identified for inclusion in the clinical utility review and so no results can be reported.

Assessment of Cost-effectiveness

Search Strategy

Full details of the main search strategy conducted by the EAG are presented in the "Assessment of Clinical Effectiveness" above. The EAG did not use specific economics-related search terms in the main strategy as all of the potential references were scanned for studies containing economic evidence.

Inclusion and Exclusion Criteria

Three reviewers independently screened all titles and abstracts identified via searching and set aside the sub-set of records with the term "cost" or "economic" included in the title or abstract (Stage 1). At Stage 2, two reviewers independently screened the titles and abstracts of the records that were potentially relevant to the cost-effectiveness review. Full paper manuscripts of any titles and abstracts that were considered relevant by either reviewer were obtained. The relevance of each study was then assessed according to the criteria set out in the table below. Studies that did not meet the criteria were excluded. Any discrepancies were resolved by consensus and, where necessary, a third reviewer was consulted.

Table. Inclusion and Exclusion Criteria

	Inclusion Criteria	Exclusion Criteria
Intervention or comparator	PCA3, Prostate Health Index (PHI)	
Study design	Full economic evaluation	Methodological paper, letter,* abstract**
Perspective	U.K or European perspective	Non-European perspective
Population	Men suspected of having prostate cancer who had had at least one negative or equivocal biopsy	Screening population

*Letters were included if they were related to a study already included in the review.

**Abstracts were judged for inclusion at the very end of the inclusion process in order to ascertain whether sufficient information was available for the abstract to be included in the review.

No published papers were identified that met the inclusion criteria for the review.

Number of Source Documents

Clinical Effectiveness

Analytic Validity Review

A total of 2249 unique records were identified by database searching and via the use of additional resources (e.g., trial registers and backward citation searching). 2021 records were excluded at the title and abstract screening stage. 228 studies were reviewed in full text and six papers were considered to be relevant for inclusion in the analytic validity review. (See Figure 1 of the Assessment Report [see the "Availability of Companion Documents" field].)

Clinical Validity Review

- Within-study comparisons: A total of 2249 unique records were identified by database searching and via the use of additional resources (e.g., trial registers and backward citation searching). 2021 records were excluded at the title and abstract screening stage due to ineligible study population (e.g., initial biopsy population only) or ineligible design. A total of 228 studies were reviewed in full text and 25 papers were considered to be eligible for inclusion in the review of clinical validity. (See Figure 1 in the Assessment Report).
- Between-study comparisons: Six papers reporting five systematic reviews and meta-analyses were identified which met the inclusion criteria. These reviews are summarised for completeness in Table 28 in the Assessment Report. The External Assessment Group (EAG) notes that none of these reviews consider clinically relevant comparisons.

Clinical Utility Review

No studies were identified for inclusion in the clinical utility review.

Cost-effectiveness

- After de-duplication, the 2249 remaining titles and abstracts (where available) were screened for inclusion at Stage 1. Of these, 2146 references were immediately excluded because they did not include the term "cost" or "economic" in either title or abstract. The remaining 103 records were assessed for eligibility and 99 were excluded as they did not include the relevant comparators or they did not consider an eligible study population. Full texts were obtained for four references. However, none of the four references met the study inclusion criteria and were, therefore, excluded from the systematic review. The PRISMA flow diagram for the cost-effectiveness review is shown in Figure 4 of the Assessment Report.
- An economic model was submitted by the EAG.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this diagnostics guidance and prepare a Diagnostics Assessment Report (DAR). The DAR for this diagnostic guidance was prepared by the Liverpool Reviews and Implementation Group (LRiG), University of Liverpool (see the "Availability of Companion Documents" field).

Assessment of Clinical Effectiveness

Analytic Validity Review

Data Extraction and Quality Assessment Strategy

Data extraction and quality assessment were undertaken by two reviewers, with disagreements resolved by discussion. Data extraction included details of source population, number of samples, specific methods/platforms evaluated, number of positive samples and negative controls tested, as well as reported results. Quality assessment was informed by the checklist proposed by Tuetsch and included the following:

- Quality of description of test undertaken

- Range of sample/study population tested representative of routine use
- Definition of correct answer
- Reporting of test failures

A copy of the data extraction form used in the analytic validity review is included in Appendix 3 in the Assessment Report.

Methods of Data Analysis/Synthesis

The design of the included studies and the types of outcomes reported were summarised in tabular form.

Clinical Validity Review

Data Extraction Strategy

A paper-based data extraction form was created for the clinical validity review (see Appendix 3 of the Assessment Report). These forms were revised after data had been extracted from three studies. Three reviewers, who worked independently, extracted relevant data and the data-extraction forms were cross-checked. When more than one publication reported findings from a single study, a composite data form was created. In cases where reported data appeared to be missing or unclear, clarification was sought from study authors.

Within-Study (Direct) Comparisons

Limited data (e.g., details relating to the comparator interventions, study population [including inclusion and exclusion criteria] and author conclusions) were extracted from studies that were eligible for inclusion but did not report data from a clinically relevant comparison, i.e., limited data were extracted from studies that reported the results of univariate PCA3 or univariate Prostate Health Index (PHI) versus univariate prostate-specific antigen (PSA).

Complete data were extracted from all other eligible studies. Particular attention was paid to:

- How the intervention and comparator tests were used (replacement, add-on, triage or not stated)
- Definition of positive biopsy, including grade and stage of tumour detected
- Threshold values used for intervention tests

The available data on all reported clinical validity outcomes were recorded including:

- 2x2 tables of true positive (TP), false positive (FP), false negative (FN), and true negative (TN) values
- Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratios
- Area under the curve (AUC) and sensitivity and specificity values derived from receiver operating characteristics (ROC) curves
- Multivariate odds ratios (ORs) for logistic regression

Outcomes were recorded for every reported:

- Threshold value
- Combinations or sequence of tests
- Grade of cancer

Systematic Reviews for Use in Between-Study Comparisons

Study extraction was limited to:

- Details relating to the comparator interventions
- Study population (including inclusion and exclusion criteria)
- Number of studies and participants included in meta-analyses
- Author conclusions

Quality Assessment Strategy

Quality assessment was not undertaken for studies which were eligible for inclusion but did not report data from a clinically relevant comparison. Quality assessment was not undertaken for systematic reviews for use in between-study comparisons as only the conclusions from these papers were included in the review.

The QUADAS-2, a modified version of the Quality Assessment of Diagnostic Accuracy Studies tool, was used to assess the quality of included

studies. This tool considers four domains: patient selection; index tests and comparator tests; reference standard; flow and timing. These domains were assessed both for risk of bias (whether the conduct or design of the study led to a distortion of results) and for applicability issues (whether the study reflected the population and tests used in practice). The tool content was tailored to meet the requirements for this review and a copy of the tool is displayed in Appendix 3 of the Assessment Report.

See Section 4.3.4 of the Assessment Report for information on issues that were of particular importance to this review.

Methods of Data Analysis/Synthesis

Extracted data, grouped by type of outcome, were tabulated for each comparison. Measures of difference between the comparator test pathways were calculated for the following measures:

- Comparison of AUC
- Sensitivity at set values of specificity
- Specificity at set values of sensitivity

Odds ratios from multivariate logistic regression analyses were recorded as a measure of the independence of the effect of the intervention tests.

The following sensitivity analyses were considered:

- Type of second biopsy (saturation, template or guided)
- Threshold value used for intervention test
- Different risk groups (grades or stages) of tumour detected by the second biopsy

Assessment of Cost-effectiveness

The External Assessment Group's (EAG's) *de novo* economic model uses the derived specificities for stated sensitivity levels.

Model Structure

A schematic of the diagnostic strategy used in the model is shown in Figure 5 in the Assessment Report. Following an initial negative biopsy, clinical assessment alone, or results from an alternative diagnostic strategy are used by the clinician to decide whether or not to recommend a second biopsy.

An economic model was produced which explored the use of multiparametric magnetic resonance imaging (mpMRI) before transrectal ultrasonography (TRUS) guided prostate biopsy in men with suspected prostate cancer. The EAG has assumed that all patients who are recommended for a second biopsy choose to have a biopsy and all those for whom a second biopsy is not recommended do not demand one. Patients having a biopsy may experience a short-term deterioration in quality of life (QoL); in addition, biopsies may result in complications.

In the base case, the EAG has adopted the assumption used in the Mowatt model, i.e., that patients with undiagnosed cancer, either with or without a second biopsy, will continue to have elevated PSA levels. In addition, the EAG has assumed that 25% of men without cancer will also continue to have a rising PSA level and that, at 1, 2 and 3 years respectively, 25%, 50% and 100% of patients with a rising PSA level will have a saturation biopsy. The EAG has included sensitivity analyses to explore the impact of 0%, 25%, 50% and 75% of men with a negative second biopsy entering PSA monitoring.

In addition, the following two scenario analyses have been undertaken by the EAG:

- The monitoring and second biopsy strategy used in the CG175 (Cancer Research UK, 2014) magnetic resonance imagine (MRI) model
- The monitoring strategy used in the Mowatt model

Time Horizon

As a PSA monitoring strategy can run for several years, the time horizon of the model is limited to the time that patients spend within any such strategy. The monitoring strategy is independent of the diagnostic strategies assessed in the model, so unless there is a lifetime PSA monitoring strategy the model does not require a lifetime horizon. In the base case, the PSA monitoring strategy runs for 3 years so the time horizon is also 3 years. The time horizons for the scenario analyses exploring the impact of the PSA monitoring strategies used in the CG175 MRI model and the Mowatt model are 6 years and 1 year respectively.

In addition, the following two scenario analyses were undertaken by the EAG:

- The monitoring and second biopsy strategy used in the CG175 MRI model

- The monitoring strategy used in the Mowatt model

These two scenarios can be considered to represent the "least costly" (Mowatt) and "most costly" (CG175 MRI model) PSA monitoring scenarios.

See Section 5 of the Assessment Report for additional information on cost-effectiveness analysis.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Developing Recommendations

After reviewing the evidence the Diagnostics Advisory Committee (DAC) agrees draft recommendations on the use of the technology in the National Health Service (NHS) in England. When formulating these recommendations, the Committee has discretion to consider those factors it believes are most appropriate to the evaluation. In doing so, the Committee has regard to any relevant provisions of the National Institute for Health and Care Excellence's (NICE's) Directions, set out by the Secretary of State for Health, and legislation on human rights, discrimination and equality. In undertaking evaluations of healthcare technologies, NICE takes into account the broad balance of clinical benefits and costs, the degree of clinical need of patients under consideration, any guidance issued to the NHS by the Secretary of State that is specifically drawn to the attention of NICE by the Secretary of State, and any guidance issued by the Secretary of State, and the potential for long-term benefits to the NHS of innovation.

The Committee takes into account advice from NICE on the approach it should take to making scientific and social value judgements. Advice on social value judgements is informed in part by the work of NICE's Citizens Council.

The Committee takes into account how its judgements have a bearing on distributive justice or legal requirements in relation to human rights, discrimination and equality. Such characteristics include, but are not confined to: race, gender, disability, religion or belief, sexual orientation, gender reassignment and pregnancy or maternity.

The Committee considers the application of other Board-approved NICE methods policies, such as the supplementary guidance on discounting and the end-of-life criteria, if they are relevant to the evaluation.

Because the Programme often evaluates new technologies that have a thin evidence base, in formulating its recommendations the Committee balances the quality and quantity of evidence with the expected value of the technology to the NHS and the public.

The credibility of the guidance produced by NICE depends on the transparency of the DAC's decision-making process. It is crucial that the DAC's decisions are explained clearly, and that the contributions of registered stakeholders and the views of members of the public are considered. The reasoning behind the Committee's recommendations is explained, with reference to the factors that have been taken into account.

The language and style used in the documents produced by the Committee are governed by the following principles:

- Clarity is essential in explaining how the DAC has come to its conclusions.
- The text of the documents does not need to reiterate all the factual information that can be found in the information published alongside the guidance. This needs careful judgement so that enough information and justification is given in the recommendations to enable the reader to understand what evidence the DAC considered and, if appropriate, who provided that evidence.

The Committee may take into account factors that may provide benefits to the NHS or the population, such as patient convenience. It may also consider costs and other positive or negative impacts on the NHS that may not be captured in the reference-case cost analysis, such as improved processes.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

The base-case analysis compared the number of biopsies needed, the disutility (quality-adjusted life years [QALY] loss) and costs of each of the diagnostic strategies. Adding the Prostate Health Index (PHI) or the PCA3 assay to clinical assessment produced a small increase in total biopsies compared with clinical assessment. This was accompanied by an increase in costs and a slight loss of utility compared with clinical assessment. Adding magnetic resonance imaging (MRI) to clinical assessment strategy reduced the number of biopsies needed from 1099 for clinical assessment to 520. This was a more costly strategy than clinical assessment, but resulted in a lower disutility. Strategies that included clinical assessment with MRI and either the PCA3 assay or the PHI were more costly and had only a slight effect on the number of QALYs lost.

The incremental analysis shows that all diagnostic strategies are dominated by clinical assessment, with the exceptions of clinical assessment plus MRI and clinical assessment plus MRI plus the PHI. The incremental cost-effectiveness ratio (ICER) for clinical assessment with MRI was £33,911 per QALY and £2,500,530 per QALY for clinical assessment with MRI and the PHI. Both strategies exceed the National Institute of Health and Care Excellence (NICE) maximum acceptable ICER of £30,000 per QALY gained.

Deterministic Sensitivity Analyses

Deterministic sensitivity analysis tested the impact of using assumptions from other data sources. Assumptions from two studies were included in these analyses. Clinical assessment together with the PCA3 assay was the only nondominated strategy, but the ICERs per QALY gained were £59,732 (80% sensitivity), £963,964 (90%), and £105,765 (90%). Sensitivity analysis also included increasing the rate of complications to the upper level suggested in the literature, reducing the cost of the PHI by 50%, increasing the upper level of the QALY loss from biopsy to the upper limit in the literature, assuming that 50% of cancers are missed on second biopsy and varying the proportion of patients with negative second biopsies entering prostate-specific antigen (PSA) monitoring. The costs of biopsy complications were also increased by 100%. The ICERs were stable to these changes; strategies involving the PHI or the PCA3 assay were dominated by clinical assessment, with the exception of clinical assessment together with MRI and the PHI. However, the ICERs for this strategy ranged from £1,213,727 to £2,500,530 per QALY gained compared with clinical assessment alone.

Probabilistic Sensitivity Analyses

Probabilistic sensitivity analysis was carried out using the base-case evidence and assumptions and the alternative evidence sources and sensitivity rates. The cost-effectiveness acceptability curve for the base-case analysis shows that the most cost-effective strategy, at £20,000 per QALY gained, is clinical assessment in 100% of model iterations. At a maximum acceptable ICER of £33,500 per QALY gained, approximately half of the iterations suggest that clinical assessment is the most cost-effective strategy. The remaining iterations suggest that clinical assessment with MRI is the most cost-effective strategy. At a maximum acceptable ICER of £37,000 per QALY gained, all iterations suggest that clinical assessment with MRI dominates (that is, is less expensive and more effective than) all other strategies.

Considerations

The Committee considered the results of the base-case analysis. They noted that the Diagnostic Assessment Report (DAR) indicated that, at a set sensitivity level of 90%, all diagnostic strategies were dominated by clinical assessment (that is, clinical assessment was less expensive and more effective), apart from clinical assessment with MRI with an ICER of £33,911 per QALY gained, and clinical assessment with MRI and the PHI with an ICER of £2,500,530 per QALY gained. The Committee concluded that the ICERs for all diagnostic strategies involving either the PCA3 assay or the PHI were high and lay outside the range that NICE would normally consider as cost effective. The tests were therefore unlikely to represent a cost-effective use of National Health Service (NHS) resources.

See Sections 5 and 6 of the original guideline document for additional discussion of the economic analysis.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

The National Institute for Health and Care Excellence (NICE) sends the Diagnostics Assessment Report (DAR), with any confidential material removed, to registered stakeholders for comment. Stakeholders have 10 working days to return comments. Models supporting the DAR are made available to registered stakeholders on request during this period.

NICE presents anonymised registered stakeholder comments on the DAR, along with any responses from NICE or the External Assessment

Group (EAG), to the Committee and later publishes these comments on its website.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Diagnostics Advisory Committee (DAC) considered a systematic review and an economic model prepared by an External Assessment Group.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate recommendation regarding use of PROGENSA PCA3 assay and Prostate Health Index for diagnosing prostate cancer

Potential Harms

Not stated

Contraindications

Contraindications

The instructions for use document states that the PCA3 assay should not be used for patients who are taking medication known to affect serum prostate-specific antigen (PSA) levels such as finasteride, dutasteride and leuprorelin. The effect of these medications on PCA3 gene expression has not yet been evaluated.

Qualifying Statements

Qualifying Statements

- This guidance represents the view of the National Institute for Health and Care Excellence (NICE) and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

Tools to help you put the guidance into practice and information about the evidence it is based on are also available (see also the "Availability of Companion Documents" field).

Implementation Tools

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Diagnosing prostate cancer: PROGENSA PCA3 assay and Prostate Health Index. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Jun 2. 50 p. (Diagnostics guidance; no. 17).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2015 Jun 2

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Care Excellence (NICE)

Guideline Committee

Diagnostics Advisory Committee

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Committee members are required to submit a declaration of interests on appointment, in every year of their tenure, and at each Committee meeting, in line with the National Institute for Health and Care Excellence's (NICE's) code of practice for declaring and dealing with conflicts of interest.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download in ePub or eBook formats from the NICE Web site .

Availability of Companion Documents

The following are available:

- Diagnosing prostate cancer: PROGENSA PCA3 assay and Prostate Health Index. Costing statement. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Jun. 1 p. (Diagnostics guidance; no. 17). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .
- Nicholson A, Mahon J, Boland A, Beale S, Dwan K, Fleeman, N, Hockenhull, J, Dundar, Y. The clinical and cost-effectiveness of PROGENSA PCA3 Assay and the Prostate Health Index (PHI) in the diagnosis of prostate cancer: a systematic review and economic evaluation. Diagnostics Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence. Liverpool (UK): Liverpool Reviews and Implementation Group, University of Liverpool; 2014 Oct. 224 p. Electronic copies: Available from the NICE Web site .
- Diagnostics Assessment Programme manual. London (UK): National Institute for Health and Care Excellence; 2011 Dec. 130 p. Electronic copies: Available from the NICE Web site .

Patient Resources

The following is available:

- Diagnosing prostate cancer: PROGENSA PCA3 assay and Prostate Health Index. Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Jun. (Diagnostics guidance; no. 17). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .

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